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**US-A- 4 383 999
US-A- 4 514 414**

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Description

Summary of the invention

5 The present invention relates to novel N-(butenyl substituted) azaheterocyclic carboxylic acids of the general formula I



10 where in R^1 and R^2 are the same or different and each represents furanyl, thienyl, pyridyl or pyrrolyl each of which may be substituted one, two or three times by halogen or lower alkyl, and R^3 represents 3-carboxypiperidin-1-yl, 3-carboxy-1,2,5,8-tetrahydropyrid-1-yl or 3-carboxymethylpiperidin-1-yl, or salts thereof.

Background of the invention

20 In the last decade, intensive pharmacological research concerning γ -aminobutyric acid (hereinafter designated GABA), a neurotransmitter in the central nervous system, has taken place.

Increased GABAergic activity is useful in the treatment of anxiety, epilepsy and muscular and movement disorders. Furthermore, these compounds can be used as sedatives.

25 In U.S. patent specification No. 4,383,999 (Smithkline Beckmann Corporation) some derivatives of N-(4-phenylbuten-3-yl)azaheterocyclic carboxylic acids which have, furthermore, inter alia, phenyl, 4-fluorophenyl, cyclohexyl or thienyl in the 4-position, are described. It is stated therein that the compounds are useful as inhibitors of GABA uptake.

30 In US Patent Specification No. 4,514,414 (Smithkline Beckman Corporation), there are described some more derivatives of N-(4-phenylbuten-3-yl)azaheterocyclic carboxylic acids. It is stated therein that the compounds are useful as inhibitors of GABA uptake.

According to J.Pharm.Exp.Therap., 228 (1984), 109 et seq., N-(4,4-diphenyl-3-butenyl)nipecotic acid (designated SK&F 89978A), N-(4,4-diphenyl-3-butenyl)guvacine (designated SK&F 100330A), N-(4,4-diphenyl-3-butenyl)- β -homoprolin (designated SK&F 100561) and N-(4-phenyl-4-(2-thienyl)-3-butenyl)nipecotic acid (designated SK&F 100604J) are active inhibitors of GABA uptake.

Detailed practice of this invention

40 It has now been found that novel compounds of the general formula I stated in Claim 1 below exhibit GABA uptake inhibitory properties and exert useful pharmacological effects on the central nervous system, i.e., a selective enhancement of GABA activity. Surprisingly, these effects are superior to those of previously known compounds. Compounds of formula I may be used for treatment of, for example, pain, anxiety, epilepsy, certain muscular and movement disorders, other neurological disorders and as sedatives and hypnotics.

45 Herein furanyl is 2-furanyl or 3-furanyl, thienyl is 2-thienyl or 3-thienyl, pyridyl is 2-pyridyl, 3-pyridyl or 4-pyridyl and pyrrolyl is 2-pyrrolyl or 3-pyrrolyl. Furthermore, halogen is, preferably, chloro, bromo and fluoro. The lower alkyl group contains less than 8 carbon atoms, preferably less than 5 carbon atoms, and some especially preferred alkyl groups are methyl and ethyl. Examples of preferred substituents R^1 and R^2 are 3-methylthienyl, 4-methylthienyl and N-methylpyrrolyl.

Compounds of formula I are, for example:

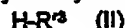
50 N-(4,4-di(furan-2-yl)but-3-enyl)nipecotic acid,
N-(4,4-di(furan-3-yl)but-3-enyl)nipecotic acid,
N-(4,4-di(thien-2-yl)but-3-enyl)nipecotic acid,
N-(4,4-di(thien-3-yl)but-3-enyl)nipecotic acid,
N-(4-(5-chlorothien-2-yl)-4-(thien-2-yl)but-3-enyl)nipecotic acid,
N-(4,4-di(pyrid-3-yl)but-3-enyl)nipecotic acid,
55 N-(4,4-di(5-methylpyrrol-2-yl)but-3-enyl)nipecotic acid,
N-(4-(furan-2-yl)-4-(thien-2-yl)but-3-enyl)nipecotic acid,
N-(4-(furan-3-yl)-4-(thien-3-yl)but-3-enyl)nipecotic acid,
N-(4-(furan-2-yl)-4-(thien-3-yl)but-3-enyl)nipecotic acid,

N-(4-(furan-3-yl)-4-(thien-2-yl)but-3-enyl)nipecotic acid,
 N-(4,4-di(furan-2-yl)but-3-enyl)guvacine,
 N-(4,4-di(furan-3-yl)but-3-enyl)guvacine,
 N-(4,4-di(thien-2-yl)but-3-enyl)guvacine,
 5 N-(4,4-di(thien-3-yl)but-3-enyl)guvacine,
 N-(4,4-di(pyrid-4-yl)but-3-enyl)guvacine,
 N-(4-(furan-2-yl)-4-(thien-2-yl)but-3-enyl)guvacine,
 N-(4-(furan-3-yl)-4-(thien-3-yl)but-3-enyl)guvacine,
 N-(4-(furan-2-yl)-4-(thien-3-yl)but-3-enyl)guvacine,
 10 N-(4-(furan-3-yl)-4-(thien-2-yl)but-3-enyl)guvacine,
 N-(4,4-di(furan-2-yl)but-3-enyl)- β -homoproline,
 N-(4,4-di(furan-3-yl)but-3-enyl)- β -homoproline,
 N-(4,4-di(thien-2-yl)but-3-enyl)- β -homoproline,
 N-(4,4-di(thien-3-yl)but-3-enyl)- β -homoproline,
 15 N-(4-(furan-2-yl)-4-(thien-2-yl)but-3-enyl)- β -homoproline,
 N-(4-(furan-3-yl)-4-(thien-3-yl)but-3-enyl)- β -homoproline,
 N-(4-(furan-2-yl)-4-(thien-3-yl)but-3-enyl)- β -homoproline,
 N-(4-(furan-3-yl)-4-(thien-2-yl)but-3-enyl)- β -homoproline,
 N-(4,4-di(3-methylthien-2-yl)but-3-enyl)guvacine,
 20 N-(4,4-di(3-methylthien-2-yl)but-3-enyl)nipecotic acid,
 N-(4,4-di(3-methylthien-2-yl)but-3-enyl)- β -homoproline,
 N-(4-(3-methylthien-2-yl)-4-(thien-2-yl))but-3-enyl-guvacine,
 N-(4-(3-methylthien-2-yl)-4-(thien-2-yl))but-3-enyl-nipecotic acid,
 N-(4-(3-methylthien-2-yl)-4-(thien-2-yl))but-3-enyl- β -homoproline,
 25 N-(4-(N-methyl-pyrrol-2-yl)-4-(thien-2-yl))but-3-enyl-guvacine,
 N-(4-(N-methyl-pyrrol-2-yl)-4-(thien-2-yl))but-3-enyl-nipecotic acid,
 N-(4-(N-methyl-pyrrol-2-yl)-4-(thien-2-yl))but-3-enyl- β -homoproline,
 N-(4,4-di(N-methyl-pyrrol-2-yl)but-3-enyl)guvacine,
 N-(4,4-di(N-methyl-pyrrol-2-yl)but-3-enyl)nipecotic acid,
 30 N-(4,4-di(N-methyl-pyrrol-2-yl)but-3-enyl)- β -homoproline,
 N-(4-(3-bromo-thien-2-yl)-4-(thien-2-yl))but-3-enyl-nipecotic acid,
 and salts thereof.

35 Compounds of formula I may exist as geometric and optical isomers and all isomers and mixtures thereof are included herein. Isomers may be separated by means of standard methods such as chromatographic techniques or fractional crystallisation.

One embodiment of this invention is non-toxic pharmaceutically acceptable salts of compounds of formula I. Salts include those derived from inorganic or organic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, lactic, maleic and phthalic acid. Furthermore, salts include salts of the carboxylic acid group, for example sodium, potassium, calcium and magnesium salts and salts with a strong base such as triethylamine.

40 Compounds of formula I may be prepared by N-alkylation of a compound of the general formula II



wherein R^3 has the same meaning as the above R^2 with the proviso that the carboxy group is protected (for example, as an ester group), with a compound of the general formula III



50 wherein R^1 and R^2 are as defined in Claim 1, and X represents halogen. This reaction may be carried out in an inert solvent in the presence of an alkali metal carbonate, for example, potassium carbonate, for example, at reflux temperature or lower temperature, for from about 8 to 24 hours. The solvent may conveniently be an alcohol, acetone or N,N-dimethylformamide. Thereafter, compounds of formula I may be prepared by hydrolysis of the resulting ester, for example by refluxing a mixture of an aqueous sodium hydroxide solution and an alcohol such as methanol or ethanol for from about 1 to 4 hours.

Compounds of formula III may be prepared by reacting the corresponding disubstituted ketones of the general formula V



wherein R^1 and R^2 each is as defined above, with a Grignard reagent, i.e., cyclopropyl magnesium bromide, followed by ring opening and dehydration of the intermediate carbinol derivative by treatment with hydrogen bromide in acetic acid.

Compounds of formula I are useful because they possess pharmacological activity in man. In particular, the compounds of formula I are useful as inhibitors of GABA uptake.

For the above indications, the dosage will vary depending on the compound of formula I employed, on the mode of administration and on the therapy desired. However, in general, satisfactory results are obtained with a dosage of from about 15 mg to about 2 g of compounds of formula I, conveniently given from 1 to 5 times daily, optionally in sustained release form. Usually, dosage forms suitable for oral administration comprise from about 25 mg to about 1 g of the compounds of formula I admixed with a pharmaceutical carrier or diluent. No toxic effects have been observed at these levels.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit approximately the same order of activity as the free base forms.

This invention also relates to pharmaceutical compositions comprising a compound of formula I or a pharmaceutically acceptable salt thereof and, usually, such compositions also contain a pharmaceutical carrier or diluent. The compositions of this invention may be prepared by conventional techniques to appear in conventional forms, for example, capsules or tablets.

The pharmaceutical carrier employed may be conventional solid or liquid carriers. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate and stearic acid. Examples of liquid carriers are syrup, peanut oil, olive oil and water. Similarly, the carrier or diluent may include any time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier for oral administration is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but, usually, will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may appear in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension.

The pharmaceutical compositions of this invention can be made following the conventional techniques of the pharmaceutical industry involving mixing, granulating and compressing or variously mixing and dissolving the ingredients as appropriate to give the desired end product.

The route of administration may be any route which effectively transports the active compound to the appropriate or desired place, such as orally or parenterally, the oral route being preferred.

Any novel feature or combination of features described herein is considered essential.

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which, however are not to be construed as limiting. The examples illustrate some preferred embodiments.

Example 1

a) To a suspension of 1.3 g of magnesium in 20 ml of anhydrous tetrahydrofuran, 8.0 g of cyclopropyl bromide in 15 ml of anhydrous tetrahydrofuran was added under nitrogen. The reaction mixture was kept under reflux for 1 hour and then cooled to ambient temperature. To the reaction mixture, 5.4 g of di(thien-2-yl)ketone dissolved in 15 ml of anhydrous tetrahydrofuran was added dropwise. After refluxing for 30 minutes, the reaction mixture was chilled and 35 ml of a concentrated ammonium chloride solution was carefully added. To the resulting mixture, 50 ml of water was added and the suspension was extracted twice with 50 ml of ether. The ether extracts were washed with water, dried and evaporated leaving 7.6 g of an oil.

The crude product was dissolved in 60 ml of acetic acid and a mixture of 30 ml of acetic acid and 15 ml of 48% hydrobromic acid was added at 5°C. The mixture was stirred for 30 minutes and then poured into 300 ml of water. The resulting emulsion was extracted twice with 100 ml of ether. The ether extracts were washed with water, dried and evaporated leaving 8.5 g of an oil.

From this oil, 5.2 g of 4,4-di(thien-2-yl)but-3-enyl bromide having a boiling point (hereinafter b.p.) of 137°C (0.05 mm Hg) was obtained by fractional distillation in vacuum.

b) A suspension of 5.0 g of 4,4-di(thien-2-yl)but-3-enyl bromide, 3.4 g of nipecotic acid ethyl ester and 3.3 g of potassium carbonate in 150 ml of dry acetone was kept under reflux for 15 hours. The reaction mixture was evaporated and, after addition of 30 ml of water, the resulting solution was extracted twice with 50 ml of ethyl acetate. The ethyl acetate extracts were dried and evaporated leaving 7.3 g of an oil. By column chromatography on silica gel using methanol as eluent, N-(4,4-di(thien-2-yl)but-3-enyl)nipecotic acid ethyl ester

was isolated.

5.3 g of this compound was dissolved in 100 ml of ethanol and 200 ml of an 8 N sodium hydroxide solution was added. The mixture was heated at reflux for 1 hour, cooled and acidified by adding 10% hydrochloric acid. The resulting solution was evaporated and 100 ml of water was added to the residue. The resulting acid solution was extracted with ethyl acetate and the dried extract was evaporated to give N-(4,4-di(thien-2-yl)buten-3-yl)nipecotic acid which after crystallization from ethyl acetate had a melting point (hereinafter m.p.) of 62 - 64°C (decomposition).

Example 2

A solution of 34 ml of n-butyllithium in 30 ml of anhydrous ether was cooled to -85°C under nitrogen and 5.3 ml of 3-bromothiophen in 10 ml anhydrous ether was added dropwise over a period of 10 min. The reaction mixture was stirred at -85°C for 1 hour and 2.7 ml of ethyl 4-bromo-butyrate in 10 ml of anhydrous ether was added slowly. The reaction was stirred for 4 hours while the temperature raised to -20°C. 20 ml water was added and the mixture was stirred for 5 minutes after which the aqueous layer was removed. The ether layer was washed with 20 ml of water and the combined aqueous phases were extracted with 50 ml of ether. The combined organic phases were dried over anhydrous sodium sulfate which after evaporation yielded 9 g of 1-bromo-4,4-di(3-methylthien-2-yl)but-3-en as an oil. This compound was without further purification used for coupling with ethyl nipecolate following the procedure according to b) in Example 1 whereby N-(4,4-di(3-methylthien-2-yl)but-3-en)nipecotic acid hydrochloride was obtained.
 $R_f = 0.38$ (MeOH; silicagel)

Examples 3 - 9

The compounds of formula I stated in table I, below, were prepared analogously to the method described in Example 1 (method A) and Example 2 (method B).

Table I

Exam- ple	R ₁	R ₂	R ₃	m.p. °C
3	4-methylthien-2-yl	4-methylthien-2-yl	nipicotic acid	60-63
4	5-methylthien-2-yl	5-methylthien-2-yl	nipicotic acid	72-76
5	thien-2-yl	3-methylthien-2-yl	nipicotic acid	86-88
6	thien-2-yl	3-methylthien-2-yl	guvacine	84-88
7	N-methylpyrrol-2-yl	N-methylpyrrol-2-yl	nipicotic acid	44
8	5-chloro-4-methylthien-2-yl	5-chloro-4-methylthien-2-yl	nipicotic acid	78-82
9	thien-2-yl	3-methylthien-2-yl	β -homoproline	oil

In Examples 5, 6 and 11, Method A was used and in the remaining examples, Method B was used. The compounds prepared were hydrochlorides (HCl).

Example 105 Preparation of Capsules.

<u>Ingredients</u>	<u>Mg per Capsule</u>
N-(4,4-di(thien-2-yl)but-3-enyl)nipecotic acid	125
Magnesium stearate	2
10 <u>Lactose</u>	<u>200</u>

15 The above ingredients are thoroughly mixed and placed into hard gelatin capsules. Such capsules are administered orally to subjects in need of treatment from 1 - 5 times daily to enhance GABAergic activity in the central nervous system.

Example 1120 Preparation of Tablets.

<u>Ingredients</u>	<u>Mg per Tablet</u>
N-(4,4-di(thien-2-yl)but-3-enyl)nipecotic acid	200
25 Corn starch	46
Polyvinyl pyrrolidone	12
Magnesium stearate	1

30 The compound is thoroughly mixed with two thirds of the corn starch and granulated. The granules obtained are dried, mixed with the remaining ingredients and compressed into tablets.

35 The capsules or tablets thus prepared are administered orally. Similarly, other compounds of formula I can be used.

Pharmacological test

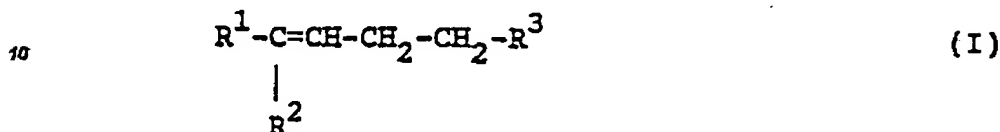
40 GABA-uptake was measured essentially as described by Fjalland (Acta Pharmacol. et. toxicol. (1978), 42, 73 - 78) using 25 mM of 3H-GABA as substrate. The results obtained appears from the following table.

<u>Compound</u>	<u>IC₅₀ (nM)</u>
45 SKF 100330 A	380
<u>N</u> -(4,4-di(3-methylthien-2-yl)buten-3-yl)- nipecotic acid, HCl	90
<u>N</u> -(4-(thien-2-yl)-4-(3-methylthien-2-yl)- 50 buten-3-yl)- β -homoproline, HCl	70
<u>N</u> -(4,4-di(<u>N</u> -methylpyrrol-2-yl)buten-3-yl)- nipecotic acid, HCl	60
55 <u>N</u> -(4-(thien-2-yl)-4-(3-methylthien-2-yl)- buten-3-yl)nipecotic acid, HCl	110

The obtained values are means from 2 separate experiments using 3 - 5 different concentrations of test compound.

5 Claims

1. 1-Aminobut-3-en derivatives of formula I



wherein R^1 and R^2 are the same or different and each represents furanyl, thienyl, pyridyl or pyrrolyl each of which may be substituted one, two or three times by halogen or lower alkyl, which contains less than 8 carbon atoms, and R^3 represents 3-carboxypiperidin-1-yl, 3-carboxy-1,2,5,6-tetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl, or salts thereof.

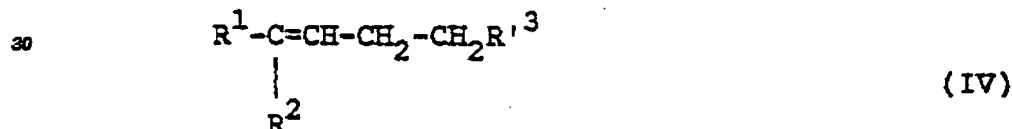
2. Derivatives according to claim 1, characterized in that the substituents are chloro or methyl.

3. Derivatives according to claim 1 or 2, wherein R^1 and R^2 each is thienyl optionally substituted by lower alkyl.

4. Pharmaceutical compositions containing a compound of formula I stated in any one of the preceding claims.

5. Compositions according to claim 4, characterized in that they contain from about 25 mg to about 1 g of the compound.

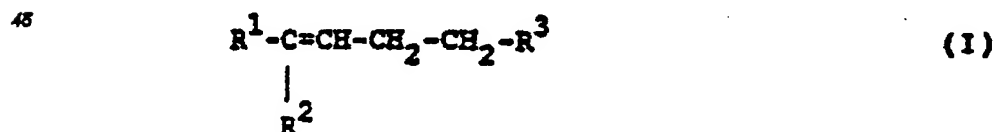
6. A process for preparing compounds of formula I stated in claim 1 or a salt thereof, characterized in hydrolysing a compound of the general formula IV



wherein R^1 and R^2 each are as defined above and R'^3 has the same meaning as the above R^3 with the proviso that the carboxy group is protected, and, if desired, converting a compound of formula I into a salt thereof or converting a salt into a compound of formula I.

40 Patentansprüche

1. 1-Aminobut-3-en-Derivate der Formel I



In der R^1 und R^2 identisch oder verschieden sind und jeweils Furanyl, Thienyl, Pyridyl oder Pyrrolyl darstellen, von denen jedes ein-, zwei-, oder dreimal mit Halogen oder niederem Alkyl, das weniger als 8 Kohlenstoffatome enthält, substituiert sein kann, und R^3 3-Carboxypiperidin-1-yl, 3-Carboxy-1,2,5,6-tetrahydropyrid-1-yl oder 3-Carboxymethylpyrrolidin-1-yl darstellt, oder Salze derselben.

2. Derivate nach Anspruch 1, dadurch gekennzeichnet, daß die Substituenten Chlor oder Methyl sind.

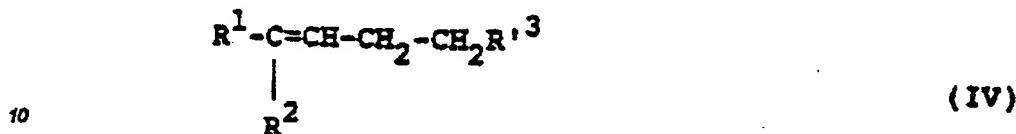
3. Derivate nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß R^1 und R^2 jeweils Thienyl sind, fakultativ substituiert mit niederem Alkyl.

4. Pharmazeutische Zusammensetzungen, die eine Verbindung der Formel I, wie in einem der vorange-

henden Ansprüche angegeben, enthalten.

5. Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß sie von etwa 25 mg bis etwa 1 g der Verbindung enthalten.

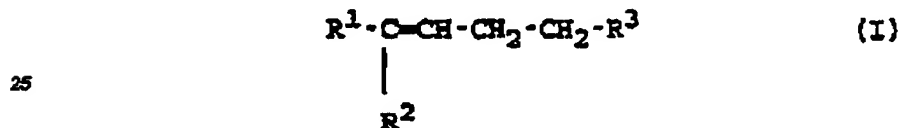
6. Verfahren zur Herstellung von Verbindungen der Formel I, wie in Anspruch 1 angegeben, oder eines Salzes derselben, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel IV



In der R¹ und R² jeweils so wie oben definiert sind und R³ dieselbe Bedeutung wie obiges R³ hat, mit dem Vorbehalt, daß die Carboxygruppe geschützt ist, hydrolisiert wird und, falls gewünscht, eine Verbindung der Formel I in ein Salz derselben überführt oder ein Salz in eine Verbindung der Formel I überführt wird.

Revendications

1. Dérivés de 1-amino-3-butène de formule 1



dans laquelle R¹ et R² sont identiques ou différents et représentent chacun un groupe furanyle, thiényle, pyridyle ou pyrrolyle pouvant être chacun substitué une, deux ou trois fois par un atome d'halogène ou un groupe alkyle inférieur qui contient moins de 8 atomes de carbone, et R³ représente un groupe 3-carboxy-1-pipéridinyle, 3-carboxy-1,2,5,6-tétrahydro-1-pyridyle ou 3-carboxyméthyl-1-pyrrolidinyle, ou leurs sels.

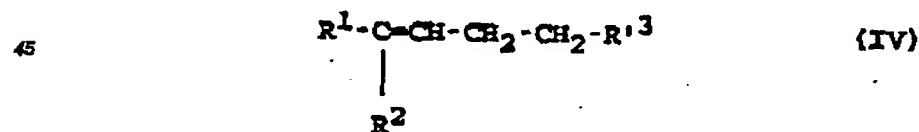
2. Dérivés selon la revendication 1, caractérisés en ce que les substituants sont des atomes de chlore ou des groupes méthyle.

3. Dérivés selon la revendication 1 ou 2, dans lesquels R¹ et R² représentent chacun un groupe thiényle éventuellement substitué par un groupe alkyle inférieur.

4. Compositions pharmaceutiques contenant un composé de formule I selon l'une quelconque des revendications précédentes.

5. Compositions selon la revendication 4, caractérisées en ce qu'elles contiennent d'environ 25 mg à environ 1 g de composé.

6. Procédé de préparation de composés de formule I selon la revendication 1 ou d'un sel de ceux-ci, caractérisé par l'hydrolyse d'un composé de formule générale IV



dans laquelle R¹ et R² sont tels que définis ci-dessus et R³ a la même signification que R³ ci-dessus avec la condition que le groupe carboxyle est protégé et, si on le souhaite, la conversion d'un composé de formule I en l'un de ses sels ou la conversion d'un sel en un composé de formule I.